Penis Malformations

- Hypospadias
- Epispadias
- Phimosis
- Phimosis

Why is it important?
- Urinary tract obstruction → ascending urinary tract infections
- Problems with ejaculation and insemination → sterility
Hypospadias

HYPOSPADIAS - urethral opening on the ventral surface (1 in 300)

Epispadias

EPISPADIAS - urethral opening on the dorsal surface

- PHIMOSIS - prepuce cannot be retracted
  Poor hygiene → infections → phimosis → infections → ? Carcinoma

- PARAPHIMOSIS - phimotic prepuce is forcibly retracted → constriction and swelling → pain → acute urinary retention
**Penis Infections (STD's)**

- **GONORRHEA** - *Neisseria gonorrhoeae* (Gram - diplococcus) - urethral strictures → sterility and ectopic pregnancies
- **CHLAMYDIA** - *C. trachomatis* - nongonorreal urethritis (Gram- intracellular)(M>F), lymphogranuloma venereum (small epidermal vesicle → ulcer → inguinæ lymphadenopathy) and trachoma (chronic keratoconjunctivitis)
  - Reiter syndrome - conjunctivitis, polyarthritis and genital infection
- **SYPHILIS** - *Treponema pallidum* (spirochete) -
  - 1 (3 weeks) - chancre
  - 2 (2-10 weeks) - palmar, solar rash, lymphadenopathy, arthritis, headache, fever, Condyloma lata
  - 3 (years) - neurysphils, aortitis, gummas

- **Herpes Simplex**
  - HSV-1 (gingivostomatitis)
  - HSV-2 (genital herpes)

- **Molluscum Contagiosum**
  - DNA poxvirus
  - There are four types of MCV-1 to -4:
    - MCV-1 is the most prevalent and MCV-2 is seen usually in adults and often sexually transmitted.
    - MCV can affect any area of the skin but is most common on the trunk of the body, arms, and legs.
    - Spread through direct contact or shared items such as clothing or towels.
**Penis Tumors**

- **Condyloma Acuminatum (Venereal wart)**
  - **Etiology:** Human papilloma virus (HPV), types 6 and 11
  - **Gross** - single or multiple sessile or pedunculated, red papillary excrescencies, one - several mm
  - **Micro** - Papillary proliferation of squamous cells. Koilocytosis - clear vacuolization of the cytoplasm

- **Penis Squamous cell carcinoma**
  - < 1% of cancers in males
  - **Risk factors**
    - poor hygiene and phimosis - accumulation of smegma, and history of genital warts
    - Circumcision confers protection
  - **Etiology:** High risk HPV types (16 and 18 most common)
  - **Gross** - Ulcerative, fungating, papillary lesions
  - **Micro** - Resembling squamous epithelium, intercellular bridges and keratin pearls

**Question**

Your next door neighbor's kid who is in college heading off to spring break in Cancun, found out you are attending medical school. He/she asks you if you know anything about HPV and condoms. Specifically he/she would like to know if condoms prevent HPV infection. You say:

A. "Yes it does."
B. "No it doesn't."
C. "You're not sure, after all you're only in the second year."
A 29-year-old man presents with these lesions in the shaft of his penis. What is the most likely causative agent?

A. Spirochete
B. Gram negative diplococci
C. Virus - poxvirus family
D. Virus - herpesvirus family
E. Virus – papillomavirus family

**Testis and scrotum -Histology**

- Serosal cavity- mesothelial lined sac immediately proximal to testis and epididymis

**Testis/Scrotum - Pathology**

- **HYDROCELE** - clear fluid (transillumination)
- **HEMATOCELE** - blood (trauma, torsion)
- **CHYLOCELE** - lymph (elephantiasis)
- **SPERMATOCELE** - semen
- **VARICOCELE** - dilated veins in the spermatic cord
**Testis - Malformations**

**Undescended testis**
- Majority idiopathic, trisomy 13
- Unilateral, 25% - bilateral
- Complications - infertility and germ cell neoplasia
- **Gross** - small, firm testicle
- **Micro** - tubular atrophy

![Normal vs. Atrophic Testis](image)

**Testis - Infection**

**Epididymitis and orchitis**
- **VIRAL** - Mumps, Coxsackie B
- **BACTERIAL** - E. coli, (Neisseria & Chlamydia)
- **GRANULOMATOUS** - Tb, Syphilis, Leprosy, Brucellosis, Sarcoidosis
- Gonorrhea & tuberculosis → epididymis
- Syphilis → testis

![Match the pictures](image)
**Testis - Torsion**

- Twisting of the cord → thick-walled arteries patent → vascular engorgement → infarction
- Neonate: in utero/ right after birth
- Adolescent often without inciting injury. Could be due to anatomic defect where testis has increased mobility.
- Sudden severe pain
- Congestion, edema, hemorrhage → hemorrhagic infarct → fibrosis
- Surgery within 8 hrs → 80% salvage, after 10 hrs → 20% salvage

**Urologic emergency!**

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**Testicular Tumors**

- Incidence 6/100,000 (worldwide increase)
- Age group 15-34 - the most common tumor in men
- White : African American - 5:1

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**Testis - Tumors**

- **GERM CELL TUMORS**
  - One histologic pattern (40%)
  - Seminoma
  - Spermatocytic seminoma
  - Embryonal carcinoma
  - Yolk sac tumor
  - Choriocarcinoma
  - Teratomas
- Mixed germ cell tumors (60%)

- **SEX CORD - STROMAL TUMORS**
  - Leydig cell tumor
  - Sertoli cell tumor
### Testicular Tumors - Clinical Classification

- **SEMINOMA**
  - Localized to testis for long time
  - 70% stage I (at presentation)
  - Metastasis to lymph nodes
  - Radiosensitive
  - 95% cured

- **NSGCT** (nonseminomatous germ cell tumors)
  - More aggressive
  - 60% stage II and III
  - Hematogenous spread (lungs and liver)
  - Radioresistant
  - 90% complete remission and cure with aggressive chemotherapy

### Testicular Tumors - Risk factors

- Cryptorchidism – higher the testis location, higher the risk of cancer (R>L)
- Gonadal dysgenesis with Y chromosome
- Testicular feminization –
- Presence of ITGCN
- HIV infection
- Trauma is not a risk factor!

### Molecular

Isochromosome of the short arm of chromosome 12, i(12p) - 90% of invasive tumors regardless of the histological type

NEJM 1997 Bosl et al.
Germ cell tumors

CLINICAL FEATURES

- Seminoma and nonseminomatous germ cell tumors - NSGCT
- Painless enlargement of testis
- Lymphatic spread - retroperitoneal, paraaortic, mediastinal, supraclavicular LN
- Hematogenous spread - lungs, liver, brain
- Seminoma - radiosensitive, NSGCT - relatively radioresistant
- AFP - yolk sac tumor, HCG - choriocarcinoma

Intratubular germ cell neoplasia (ITGCN)

- Seen often associated with malignant germ cell tumors
- Intratubular proliferation of malignant germ cells
- Large atypical cells, abundant clear cytoplasm, central nucleus, prominent nucleoli “fried egg”

Seminoma

- The most common germ cell tumor
- Peak - 30-40 years old
- Gross - homogenous, gray-white cut surface

What is the ovarian counterpart of seminoma?
Seminoma

Histology:
- sheets of uniform, large cells with distinct cell membrane, clear cytoplasm, large central nucleolus
- Fibrous septae infiltrated with lymphocytes

Clinical: Serum bHCG could be high in 10% of the cases, AFP is normal

Embryonal Carcinoma

- Peak - 20 - 30 years old
- Gross - variegated, poorly demarcated, foci of necrosis and hemorrhage

Micro - large anaplastic cells with prominent nucleoli with indistinct cell borders arranged in solid, glandular, tubular, papillary patterns.
Yolk Sac Tumor
(Infantile embryonal carcinoma or endodermal sinus tumor)

- Two peaks: 1 - infants (good prognosis) and young adults (mixed tumors)
- Most common testicular tumor in infants up to 3 Y.
- Micro - reticular network of cuboidal cells, papillary and solid patterns (Schiller-Duval or glomeruloid bodies) and hyaline-like globules (AFP and alpha1-antitrypsin)

Schiller-Duval Body

Choriocarcinoma

- Pure form <1%, component of mixed tumors ~15%
- 2nd and 3rd decade, metastasis at presentation, highly aggressive
- Gross - small, hemorrhage and necrosis
- Micro -
  - Syncytiotrophoblast - large, vacuolated and multinucleated cell with dark eosinophilic cytoplasm, positive HCG
  - Cytotrophoblast - uniform, polygonal cell with clear cytoplasm, single nucleus and distinct cell borders

Teratoma

- Random admixture of tissue derived from ectoderm, endoderm and mesoderm
- From infancy (pure) to adulthood (mixed germ cell tumors)
- Mature, immature, with malignant transformation
- No benign teratomas in post pubertal males!!!!
**Leydig Cell Tumor**

- The most common sex cord-stromal tumor
- Any age, most common 2nd - 6th decade
- Clinical: Usually unilateral testicular enlargement, endocrine: precocious puberty, gynecomastia
- Gross - well circumscribed, ~3 - 4 cm nodule with homogenous, golden-brown cut surface
- Histology: Solid growth of large, polygonal cells with abundant granular cytoplasm and single, round, centrally located nuclei with prominent nucleoli.
- **Crystalloids of Reinke** - pathognomonic

**Lymphoma**

- Usually secondary. The most common - large B-cell lymphoma
- > 60 years old the most common testicular neoplasm (the second - metastasis to the testis)
- **Prognosis** - poor
- **GROSS**: fleshy, white gray to pink, usually replace testicular parenchyma

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<table>
<thead>
<tr>
<th>Tumor</th>
<th>Age group (most common)</th>
<th>Serum marker</th>
<th>Histologic feature</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma</td>
<td>30-40 years</td>
<td>bHCG may be</td>
<td>Uniform, large cells with clear cytoplasm</td>
<td>Most common testicular tumor</td>
</tr>
<tr>
<td>Embryonal Carcinoma</td>
<td>20-30 years</td>
<td>LH, FSH, bHCG may be</td>
<td>Large anaplastic cells</td>
<td>Rare to see pure form</td>
</tr>
<tr>
<td>Yolk Sac Tumor</td>
<td>6-18 years (pure form)</td>
<td>AFP</td>
<td>Schiller-Duval Body</td>
<td>Most common testicular tumor in infants</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>20-30 years</td>
<td>bHCG 1</td>
<td>Syncytiotrophoblast, early syncytiotrophoblast</td>
<td>Pure form seen in children, difficult to treat in adults</td>
</tr>
<tr>
<td>Testicle</td>
<td>All ages</td>
<td>LH may be</td>
<td>Cuboidal cells with varying maturation</td>
<td>Pure form seen in children</td>
</tr>
<tr>
<td>Leydig Cell Tumor</td>
<td>20-60 years</td>
<td>Cogogan may be</td>
<td>Large, polygonal cells with abundant granular cytoplasm</td>
<td>Rare's cyst (cytologic)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>&gt; 60 years</td>
<td>LDH</td>
<td>Discolored cells with high N:C ratio</td>
<td>Most common Diffuse large B-cell lymphoma</td>
</tr>
</tbody>
</table>
You are on your first day of your pathology elective as an M3 (and enjoying it already), your friendly genitourinary pathologist (whom you are signing out with) asks you lovingly – remember the histology of testis? What is this structure? You answer confidently:

A. Sertoli cell
B. Seminiferous tubule
C. Spermatic cord
D. Rete Testis
E. Is this testis? I thought is was prostate.

Which of the following serologic pattern is most specific for this 25-year-old man with a 4 cm hemorrhagic testicular mass?

A. Elevated serum LDH
B. Normal serum AFP
C. Elevated serum AFP
D. Normal serum HCG
E. Elevated serum HCG

For the USMLE

- Most common testicular tumor in adults?
- Most common bilateral primary testicular tumor?
- Most common bilateral secondary testicular tumor?
- Most common testicular cancer in infants and children?
- Most common non-germ cell tumor of the testis?
- Which are more common in the testis - mixed tumors or pure histologic types tumors?
Pathology of the Lower Urinary Tract and Male Genital System II

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Department of Pathology

Prostate

Benign Prostatic Hyperplasia

A normal prostate gland is about 3 to 4 cm in diameter, 20-30 cc volume. It is retroperitoneal and devoid of a distinct capsule.

Carcinoma

Normal prostate histology

Secretory cells

Basal cells

Normal Histology
**Prostate**

**Benign Prostatic Hyperplasia (BPH)**

- Hyperplasia of prostatic glands and stroma
- Extremely common (?normal aging process)
- 40 y. old – 20%, 60 y. old – 70%, 80 y. old – 90%
- ~ 30% - moderate to severe symptoms (mostly due to secondary effects)
  - Compression of urethra – difficulties with urination (frequency, nocturia, difficulties with starting and stopping, overflow dribbling, dysuria)
  - Retention of urine in the bladder – distention and hypertrophy, cystitis, pyelonephritis

**Gross** - Prostatic enlargement due to presence of nodules in the preprostatic region (periurethral, transitional zone)

**Micro** - Nodularity due to proliferation or dilation of glandular component and muscular proliferation of the stromal component
Prostate
Benign Prostatic Hyperplasia (BPH) – secondary changes

Bladder with hypertrophic muscularis propria resulting in trabeculations

BPH

**Pathophysiology**
- Testosterone is converted to dihydrotestosterone (DHT) in stromal cells
- DHT acts on androgen receptor in stromal and glandular cells resulting in hyperplastic nodules

**Treatment**
- 1. Alpha -1 antagonists (relaxes smooth muscle)
- 2. 5-alpha reductase inhibitor (blocks conversion of testosterone to)

Prostate cancer - Epidemiology

- Adenocarcinoma most common type
- Increased incidence - early detection
- 10% - at 50 years of age, 80% - at age of 80
- African ancestry > European ancestry > Asian ancestry
**Prostate Cancer - Molecular**

- **Androgen Receptor**: X-linked AR gene contains a polymorphic sequence composed of CAG repeats (patients with shortest CAG repeats have the highest androgen sensitivity)
- **BRCA2** germline mutation (chr 13q): 20 fold increased risk for PCA
- Somatic mutation resulting in chromosomal rearrangement placing **ETS gene** under the control of the TMPRSS2 promotor. ETS fusion genes could be detected in urine.

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**Prostate: What is PSA?**

- Serine protease composed of single-chain glycoprotein
- Secreted into seminal fluid where dissolves seminal coagulum
- Produced by epithelial cells of normal, hyperplastic and cancerous prostatic tissue
- Elevated in: prostatic ca, BPH, prostatitis, trauma, infarct, DRE, ejaculation
- Reduced by: 5α-reductase inhibitors, androgen deprivation, prostatectomy
- PSA levels increases with age
- **PSA > 4ng/ml is abnormal (n=0-4 ng/ml)**

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**Prostate Cancer Screening Guidelines**

- U.S. Preventive Services Task Force: recommends against PSA screening for prostate cancer
- **AUA Guidelines:**
  - recommends against PSA screening in men under age 40 and over age 70 years.
  - does not recommend routine screening in men between ages 40 to 54 years at average risk.
  - for men younger than age 55 years at higher risk (e.g., positive family history or African American race), decisions regarding prostate cancer screening should be individualized.
  - recommends shared decision-making for men age 55 to 69 years that are considering PSA screening.
  - Screening every 2 years rather than annually
Prostate Carcinoma

Gross Morphology

- Palpably hard, tan/white nodule
- Posterolateral portion of gland (peripheral zone)
- Most often - tumor is not grossly visible

Prostate carcinoma

Histology

- Small glands with an infiltrative pattern
- Nuclear enlargement
- Prominent nucleoli
- Single-cell layer
- Perineural invasion

Prostate Cancer

Grading System – Gleason System

- Based on architectural pattern
- Five grades – 1-5
- Gleason score: primary (dominant) grade + secondary (subdominant) grade
- International Society of Urologic Pathology
  - ISUP 1= Gleason score (3+3)
  - ISUP 2= Gleason score (3+4)
  - ISUP 3= Gleason score (4+3)
  - ISUP 4= Gleason score (4+4) or (3+5) or (5+3)
  - ISUP 5= Gleason score (4+5) or (5+4) or (5+5)

The best marker to predict prognosis

The best marker to predict prognosis
Prostate Cancer Staging

- Primary Tumor (T)
  - T1 – clinically inapparent lesion (dx on core biopsy)
  - T2 – confined to prostate
  - T3 – local extraprostatic extention
  - T4 – surrounding organs
- Lymph nodes (N) N0 / N1
- Metastasis (M) M0 / M1

Prostate Cancer Treatment

- Organ confined: Watchful waiting or Radical Prostatectomy depending on the volume and grade of tumor
- Alternative treatment for localized disease: Radiation (internal or external), Cryoablation
- Advanced/Metastatic disease: Androgen deprivation
**Prostate cancer** - bone metastases

Clinical presentation: backache

Know this:
- Prostate – Osteoblastic bone metastasis
- Renal Ca - Osteolytic bone metastasis

A 62-year-old man presents to a primary care physician for a check up. A serum PSA is performed 9ng/ml (normal 0-4 ng/ml). A transrectal prostatic biopsy is obtained, shown in the picture. What is the best clinical approach?

A. CT scan of abd/pel/thorax
B. Cystoprostatectomy
C. Repeat prostatic biopsy
D. Watchful waiting/routine follow up

**Traveling downstream**

- Ureters
- Urinary Bladder
- Urethra
You are still signing out with the genitourinary pathologist, she/he ask you what is the epithelial lining of the urinary tract? You answer:

A. Squamous epithelium  
B. Columnar epithelium  
C. Urothelial epithelium  
D. Tubular and glomerular epithelium

Urothelium - function
- Urine - blood barrier  
- Ability to dilate and contract

UROTHELIUM
- 5-7 layers
- umbrella (superficial), intermediate, and basal cells
- LAMINA PROPRIA - loose connective tissue, delicate bundles of smooth muscle fibers - muscularis mucosae
- MUSCULARIS PROPRIA - deep muscle, detrusor muscle; muscle wall arranged in several layers

Remember histology?

Adapted from Koss
**Ureter**

**Congenital abnormalities**

- Seen in 2-3% of all autopsies
- Obstruction could lead to reflux -> inflammation -> pyelonephritis
- Ureteropelvic junction obstruction - the most common cause of hydronephrosis in children
- Double ureters - double renal pelvis, bifid pelvis
- Diverticula, megaureter (defect of ureteral muscle)

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**Causes of obstruction in the Urinary Tract (UT)?**
Causes of obstruction in the Urinary Tract (UT)?

- INTRINSIC (from the inside)
  - CALCULI
  - STRICTURES
  - TUMORS
  - BLOOD CLOTS
  - NEUROGENIC

- EXTRINSIC (external to the UT)
  - PREGNANCY
  - PERIURETERAL INFLAMMATION
  - ENDOMETRIOSIS
  - RETROPERITONEAL FIBROSIS
  - TUMORS

Ureter
Malignancy

- Most common malignancy: Urothelial carcinoma (will be covered under Urinary Bladder)

Urinary Bladder
Congenital Anomalies

- DIVERTICULI
- EXSTROPHY - developmental failure in the anterior wall of the abdomen and in the bladder
- VESICOURETERAL REFLUX
Urinary Bladder
Acute and Chronic Cystitis

- Epidemiology: more common in women (short urethra)
- Predisposing factors: bladder calculi, urinary obstruction, diabetes mellitus, instrumentation, immune deficiency
- Etiology: *E. coli*, *Proteus*, *Klebsiella*, *Enterobacter*, *Staphylococcus saprophyticus*
- Gross Pathology: Hemorrhage
- Histology: Acute inflammation
- Clinical presentation: Frequency, pain (lower abdomen), dysuria (painful urination), fever

Urinary Bladder
Squamous Metaplasia
“Leukoplakia”

- Etiology: Long-term irritation or chronic infection - stones, nonfunctioning bladders, schistosomiasis
- Gross pathology: gray-white patches in the bladder
- Histology: keratinizing squamous epithelium
- Clinical Significance:
  - Extensive may interfere with contraction and dilation
  - Risk factor for carcinoma

Bladder cancer
Epidemiology and Clinical Presentation

- Epidemiology:
  - Male: Female 3:1
  - Age 50-80 Y (81%), average age of diagnosis 65
  - Bladder is the most common site for urothelial carcinoma
- Clinical Presentation:
  - Painless hematuria (80%)
  - Irritative symptoms (dysuria, frequency, urgency- mostly in high grade and invasive carcinomas)
  - Other (flank pain, bone pain, pelvic mass)
Etiology
- Cigarette Smoking ***
- Arylamines
- Chronic cystitis
  - Schistosomiasis
  - UTI
  - Indwelling catheter
  - Urolithiasis
- Cyclophosphamide- acrolein metabolite
- Long term analgesic usage (phenacetin)
- Pelvic irradiation

Remind your patients not to smoke.

Normal Urothelium
Hyperplasia
Dysplasia
Low Grade Carcinoma
High Grade Carcinoma
Carcinoma in situ
Invasive Carcinoma

Papillary Pathway 80%
Non-Papillary Pathway 20%

Genetically Stable\
FGFR3 (~85%)
Genetically Unstable\
p53 (~60%)
RAS (?)
Rb-

Urinary Bladder - Flat Lesions
Urothelial carcinoma in situ
Gross morphology/cystoscopic appearance

Which one is urothelial carcinoma in situ, which one is normal bladder?
If untreated, 50% to 75% of CIS cases progress to muscle-invasive cancer.

**Urinary Bladder**
**Urothelial carcinoma in situ**

If untreated, 50% to 75% of CIS cases progress to muscle-invasive cancer.

**Urinary Bladder- Papillary lesions**

| Papilloma   | Low grade papillary UC | High grade papillary UC |

Know this:
Low grade lesions: FGFR3 mutations
High grade carcinoma: TP53 mutations

Papillary Tumor
Normal appearing bladder mucosa
Prostate

Bladder: Gross Morphology
Invasive Urothelial Carcinoma

Staging Urothelial Tumors
Lamina propria
Muscularis propria
Urothelium
Perivesical adipose tissue
Invading adj organs
Invading abd/pelvic wall

Bladder carcinoma:
Detection and follow-up

Urine cytology combined with cystoscopic findings is the best way to follow up patients with Urothelial Carcinoma
Bladder cancer: Treatment

- Low grade small, papillary tumors - transurethral resection (TUR); follow-up (cystoscopies + cytology) for the rest of the life
- Urothelial carcinoma in situ (CIS) and papillary high-grade, T1 - intravesical immunotherapy (BCG)
- T2-4, tumors refractory to BCG, CIS in prostatic urethra - cystectomy
- Multiple tumors - intravesical chemotherapy
- Metastasis - chemotherapy

BCG - bacillus Calmette-Guérin

- Attenuated strain of Mycobacterium tuberculosis
- Intravesical BCG immunotherapy is one of the most widely used approach to manage superficial bladder cancer
- Elicits a local cell-mediated immune reaction that destroys tumor cells
- Designed to treat established disease
- Designed to prevent recurrence

Other Epithelial Tumors

- Squamous cell carcinoma
- Adenocarcinoma
- Small cell carcinoma

Schistosoma egg
**Bladder**
Mesenchymal Tumors

- Most common in **infancy**: Embryonal Rhabdomyosarcoma
- Most common in **adults**: Leiomyosarcoma

**Urethra**
Tumor and Tumor-Like Lesions

- Caruncle - inflamed granulation tissue polyp
- Peyronie disease - fibrous bands involving corpus cavernosum of the penis
- Carcinomas (proximal urothelial, distal squamous)

A 67-year old man presents with painless hematuria. The cystoscopic picture and biopsy is provided. What is the most common molecular abnormality seen in this tumor?
A. FGFR3
B. p53
C. KRAS
D. BRCA2
Questions?

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